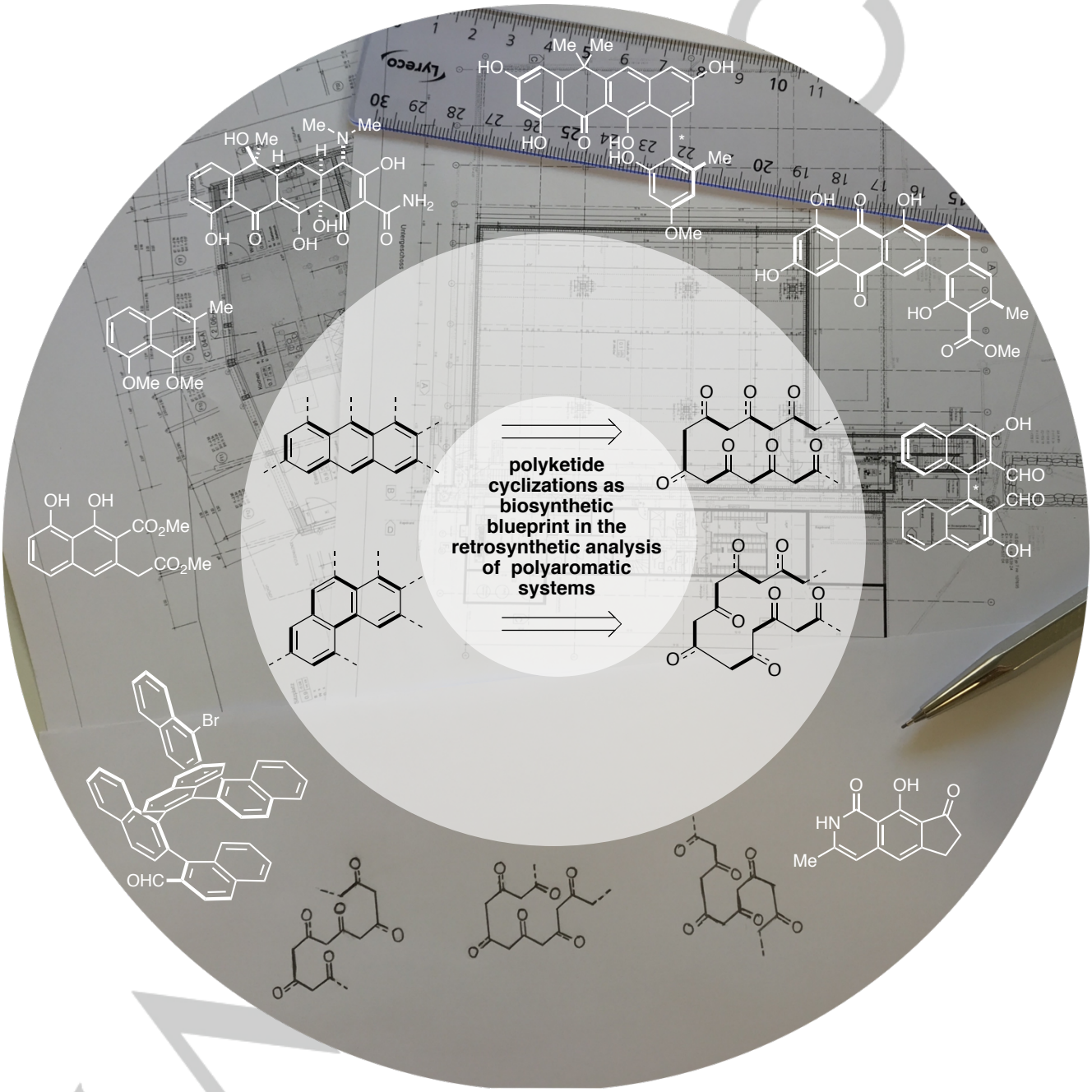
Polyketide Cyclizations for the Synthesis of Polyaromatics

Vincent C. Fäseke, Felix C. Raps, Christof Sparr*[a]



The folding and cyclization of poly-β-carbonyl chains controlled by the intricate enzymatic polyketide synthase machinery results in a remarkable diversity of aromatic natural products. Synthetic methods that allow for the preparation of highly reactive polyketide chains and control over their folding in ensuing cyclizations likewise lead to versatile divergent preparations of aromatic scaffolds valuable for numerous applications. Although biomimetic polyketide cyclizations have repeatedly been applied in the total synthesis of polyphenol natural products, their prospects for the preparation of the broad range of polyaromatic architectures has yet to reach its full potential. This review highlights some of the virtues of applying polyketide logic for the retrosynthetic analysis of polycyclic aromatic scaffolds, the increasing accessibility of precursors and the potential of small-molecule catalysts for controlling polyketide cyclizations to provide polyaromatic scaffolds.

1. Introduction

Aromatic polyketides are a vast group of structurally, biogenetically and pharmacologically intriguing natural products, isolated from bacteria, fungi and plants.[1] Several compounds of this class of natural products are indispensable for human medicine, for instance in the treatment of cancer and bacterial infections (e.g. tetracycline and doxorubicin, Figure 1a) while others have a great potential as novel drug candidates in medicinal chemistry campaigns. Intriguingly, the structural diversity of the aromatic core structures originates from common poly-β-carbonyl chain intermediates, which are assembled, processed, preorganized by their folding and cyclized by the intricate polyketide synthase (PKS) enzymatic machinery.[2] By optional tailoring processes, the aromatic systems are often further differentiated by methylation, amination, oxidation and glycosylation steps.[3] In addition to the various linear and angular aromatic systems, atropisomeric aromatic scaffolds, typically produced by oxidative phenol couplings of aromatic systems, are frequently encountered (e.g. (S_a)-ustalaginoidin A).[4] Recently, a new class of aromatic polyketide was isolated, suggesting a preorganizing folding that results in an atroposelective polyketide cyclization leading to enantioenriched biaryl entities (e.g. fasamycin C).[5] Considering the retrosynthesis of polyaromatic scaffolds in view of polyketide biosynthesis, synthetically derived poly-β-carbonyl chains epitomize the ideal substrates for accessing a diverse set of aromatic scaffolds (Scheme 1c). Biomimetic keto-processing of the poly-β-carbonyl intermediates by selective carbonyl reductions and control over folding modes to guide corresponding aldol or Claisen cyclizations, enable the preparation of numerous aromatic scaffolds bearing different oxygenation patterns and topologies.[6] Over the years, polyketide cyclizations have become a valuable synthetic strategy for the biomimetic preparation of natural products, where the folding modes are controlled by preorganized substrates in order to assemble suitable aromatic core structures. Recently, small-molecule catalysts have been applied to control stereoselective aldol condensations to provide atropisomeric aromatic scaffolds related to the biogenesis of aromatic polyketides. Catalytic polyketide cyclizations thus hold great promise for constructing novel aromatic scaffolds by emulating selective polyketide chain folding.

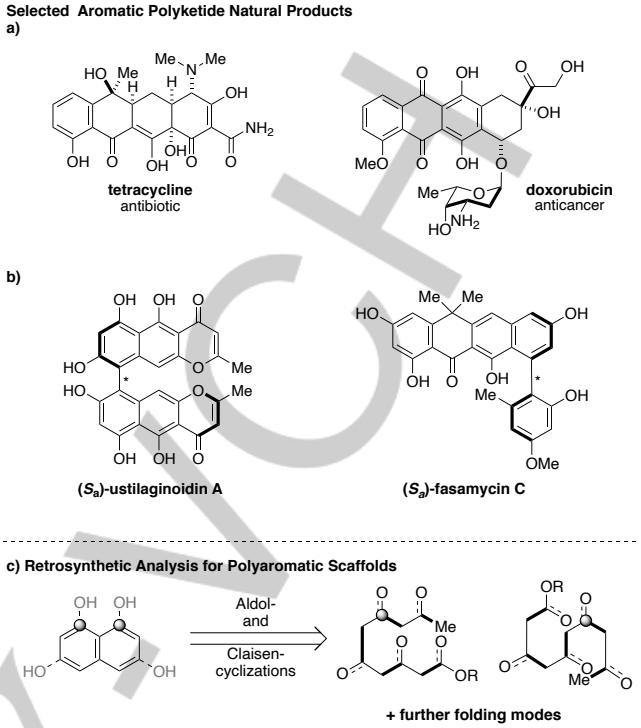


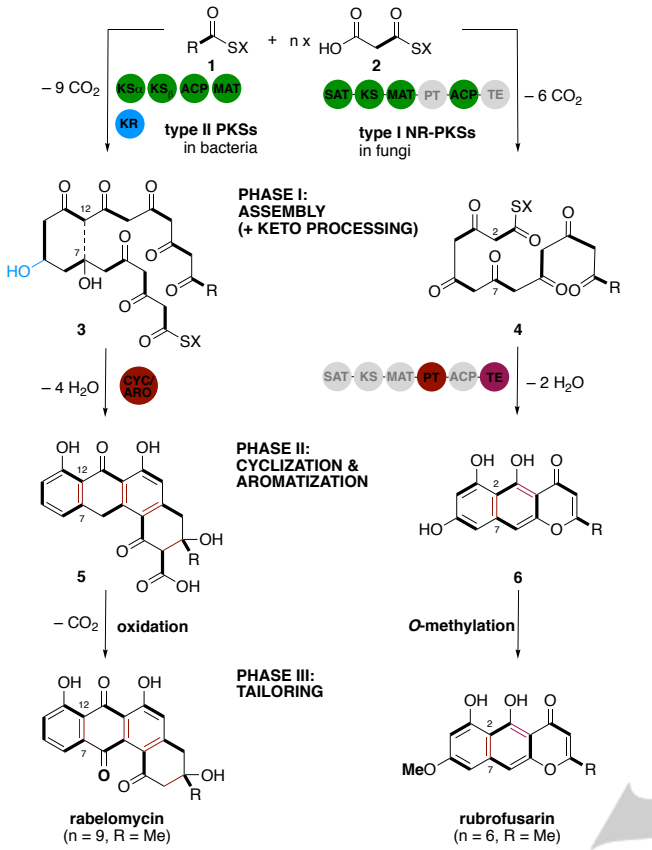
Figure 1: a) Selected aromatic polyketides used as antibiotics and cancer therapeutics. b) Atropisomeric polyketide natural products. c) Retrosynthesis of polyaromatic scaffolds by applying the logic of polyketide biosynthesis to identify conceivable pentaketide precursors, optional keto-processing, and the folding for the ensuing aldol-, Knoevenagel-, and Claisen-cyclization processes.

2. Biosynthesis of Aromatic Polyketides

Polyketide synthases (PKSs) are multi-enzyme complexes that assemble a broad range of natural products including aromatic polycycles, macrolides, polyenes and polyethers.[2] Based on their architecture and mode of action, PKSs can be classified into modular type I, and iterative type I, II and III. The iterative type I PKSs are further divided into the subgroups of highly reducing (HR-), partially reducing (PR-) and non-reducing (NR-) PKSs. Aromatic polyketide scaffolds are typically provided by type II, iterative type I NR- as well as PR- and type III PKSs.

These aromatic PKSs catalyze the iterative assembly of acetate C_2 synthons (typically condensation of malonyl units, **2**) onto a specific starter unit (primer, **1**) leading to poly-β-carbonyl chain intermediates (phase I in Scheme 1, **3**, **4**). The folding and cyclizations of these highly reactive chains controlled by the enzymatic machinery result in the formation of the corresponding aromatic core structures (phase II, **5**, **6**), which are typically further diversified by tailoring processes involving methylation, oxidation and glycosylation steps (phase III, rabelomycin and rubrofusarin).[3]

[a] V. C. Fäseke, F. C. Raps, Prof. Dr. C. Sparr
Department of Chemistry, University of Basel
St. Johanns-Ring 19, 4056 Basel (Switzerland)
E-Mail: christof.sparr@unibas.ch
Homepage: http://www.sparr.chemie.unibas.ch



Scheme 1: Proposed biosynthesis of an angulamycin (rabelomycin) by type II PKSs of bacteria and of nor-rubrofusarin by type I NR-PKSs of fungi.

The bacterial aromatic polyketide biosynthesis is mainly governed by type II PKSs, which comprise an accumulation of dissociated mono-functional enzymes (Scheme 1).[7] The poly-β-carbonyl chain is constructed by the minimal PKS, which consists of the heterodimeric keto-synthase (KS_α+KS_β), malonyl CoA-acyl carrier protein transacylase (MAT) and the acyl carrier protein (ACP). Here, the length of the assembled chain is controlled by the KS_β (chain length factor).[8] In bacteria, keto-processing of the nascent polyketide chain is performed by keto-reductases leading for instance to the regioselective C9-carbonyl reduction leading to a loss of oxygen, which is frequently observed in the oxidation pattern of tetracyclines, anthracyclines and angucyclines. The KR as well as the KS_β are proposed to already initiate the first cyclization leading to the selective C7-C12 aldol cyclization, which are then further selectively cyclized by cyclases/aromatases (CYCs/AROs).[9]

In fungi, the aromatic polyketide biosynthesis is mainly accomplished by megasynthases consisting of multiple functional tethered domains, however without KR domains (iterative type I NR-PKSs, Scheme 1).[10] The truly remarkable progress in the understanding and engineering of PKSs furthermore allows to recognize the minimal PKS, built of an keto-synthase (KS), malonyl specific acyltransferase (MAT) and the ACP.[10,11] Beside the non-reducing nature of the type I NR-PKSs different to the type II PKSs, the regioselective cyclizations of the nascent polyketide chain are initiated and controlled by the product template domain (PT) as well as the thioesterase (TE).[12]

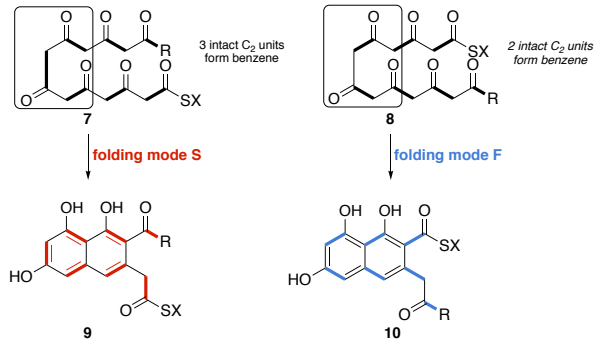
Vincent C. Fäseke received his B. Sc. degree from the University of Basel in 2013 and moved to the University of Oslo for a research internship in the group of Prof. Einar Uggerud. He completed his M. Sc. and PhD in the group of Prof. Christof Sparr working on biomimetic polyketide cyclizations. In *2019, he received a SNSF fellowship to carry out his postdoctoral research in the group of Prof. Eric N. Jacobsen at Harvard.*

Felix C. Raps completed his B. Sc. at the University of Basel in 2015. After specializing in NMR spectroscopy and chemical biology, he joined the Sparr group for his M. Sc. degree. After a research internship at Actelion/Idorsia under the supervision of Dr. C. Bürki and Dr. S. Abele, he started with his PhD work in the Sparr research group in 2017.

Christof Sparr received his PhD from the ETH Zurich working in the group of Prof. Ryan Gilmour. He then joined the groups of Prof. Dieter Seebach and Prof. Steven V. Ley. In 2013, Christof became habilitand mentored by Prof. Karl Gademann and since 2016, Christof works as Assistant Professor at the University of Basel. He is recipient of the ETH silver medal, a SNSF starting grant, the Werner Prize of the Swiss Chemical Society 2017 and the Ruzicka Prize of the ETH Zurich 2018.

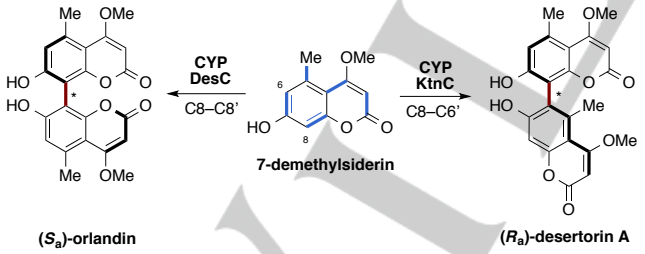
The PT typically mediates multiple aldol cyclizations in its single active cavity, which then is often followed by a Claisen cyclization controlled by the TE to release the aromatic product from the megasynthase. Beside these two PKS systems producing large aromatic polyketide core structures, the partially reducing subgroup of type I PKSs found in bacteria (type I PR-PKSs) produce smaller aromatic systems (up to naphthoic acid).[13] With the incorporated KR domains in the megasynthase, multiple selective keto-reductions of the assembled polyketide chain lead to aromatic scaffolds with a reduced level of oxygenation. In contrast, type III PKSs are mainly found in plants and consist of a homodimer KS that performs a limited number of polyketide chain elongations without keto-reduction and directly mediates the corresponding regioselective cyclizations.[14] The highly reactive polyketide chains assembled by PKSs are prone to spontaneous cyclizations and therefore, the immediate folding and the subsequent regioselective cyclizations controlled by the enzymes are assumed to be essential for the efficient construction of aromatic fused ring systems.[15] Here, the initial enzyme-controlled cyclization of the polyketide chains results in specific cyclization patterns, which allows to differentiate the aromatic core structures formed by bacteria or fungi. According to these distinct initial cyclizations, a classification of aromatic polyketides into the folding mode F (fungi, **10**) and folding mode S (*streptomyces*, **9**) has empirically been established (Scheme 2).[16]

When the initial benzene ring contains three intact acetyl C_2 units (**7**→**9**), the aromatic polyketide follows the bacterial folding mode S. Contrary, with the incorporation of two intact acetyl C_2 units (**8**→**10**), the aromatic fused-ring system is classified as the fungal folding mode F.



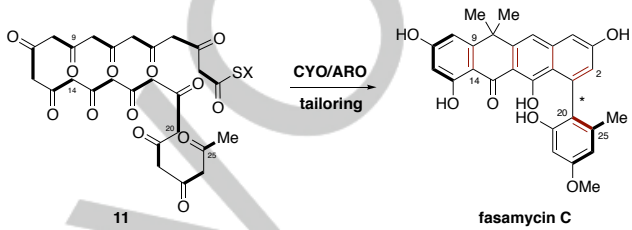
Scheme 2: Concept of the initial cyclization leading to either the folding mode S (*Streptomyces*, bacteria) and folding mode F (fungi).

In addition to the diversity of aromatic systems generated by the PKSs assembly-line processes, tailoring steps such as oxidative transformations allow for new ring topologies, for instance resulting from oxidative rearrangements.[3h] In contrast, oxidative phenol coupling reactions of previously folded and cyclized aromatic polyketides often result in tetra- or tri-*ortho* substituted biaryls with a restricted rotation about the newly formed C–C bond. These atropisomeric scaffolds are frequently found in aromatic polyketide products such as ustilaginoidin A (Figure 1b), (S_a)-orlandin or (R_a)-desertorin A (Scheme 3).[17] In biosynthetic oxidative phenol coupling processes, oxidative enzymes (OxyEnz) such as laccase, peroxidase or cytochrome P450 enzymes (CYP) are commonly involved.[3] The additional diversification of these unique stereoisomeric scaffolds can be guided by dirigent proteins that control regio- and stereoselectivity.[18] For instance, from 7-demethylsiderin, divergent oxidative regioselective dimerization by either the CYP KtnC or DesC led to the enantioselective synthesis of (+)-orlandin or (+)-desertorin A, respectively.



Scheme 3: Regio- and enantioselective oxidative biaryl coupling catalyzed by cytochrome P450 enzymes (CYP). The aromatic pentaketide 7-demethylsiderin is converted either into (S_a)-orlandin or (R_a)-desertorin A.

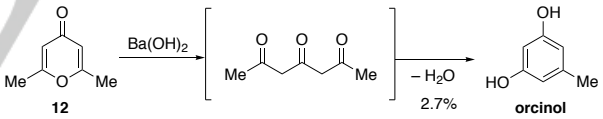
However, a recently reported class of tridecaketides emerging from a distinctive fold (**11**) indicates an alternative biosynthetic process for the stereoselective construction of atropisomeric biaryl natural products (Scheme 4).[5] In contrast to the stereoselective oxidative phenol coupling, the proposed biosynthetic pathway suggests an atroposelective aldol cyclization controlled by cyclases. According to the biosynthetic gene cluster, the hypothetical biosynthetic pathway follows the typical first three cyclizations of the decaketide tetracenomycins and the related angularly cyclized dodecaketides (C9–C14, C7–C16 and C5–C18). After these three cyclizations, a branching point is reached and the additional acetyl C_2 unit in combination with a putative cyclase/aromatase enables the cyclization of C25–C20. The subsequent proposed fifth cyclase then performs the last cross-linking of the C2–C19 in a stereoselective fashion. Final enzyme-controlled tailoring processes including methylation, decarboxylation and oxidation provide the enantioenriched, tri-*ortho*-substituted biaryl scaffold of fasamycin C (**4**).



Scheme 4: Proposed folding and cyclization mode of the tridecaketide leading to the formation of the atropisomeric fasamycin C (**4**).

3. Polyketide Cyclizations for the Synthesis of Aromatic Compounds

In 1893, J. N. Collie discovered the formation of orcinol after treatment of dimethylpyrone (**12**) under basic conditions and proposed the biosynthetic hypothesis that oxygenated aromatic natural products are assembled from poly-β-carbonyl chains derived from the condensation of acetic acid units (Scheme 5).[19,20] This hypothesis was later reexamined by Sir R. Robinson.[21]

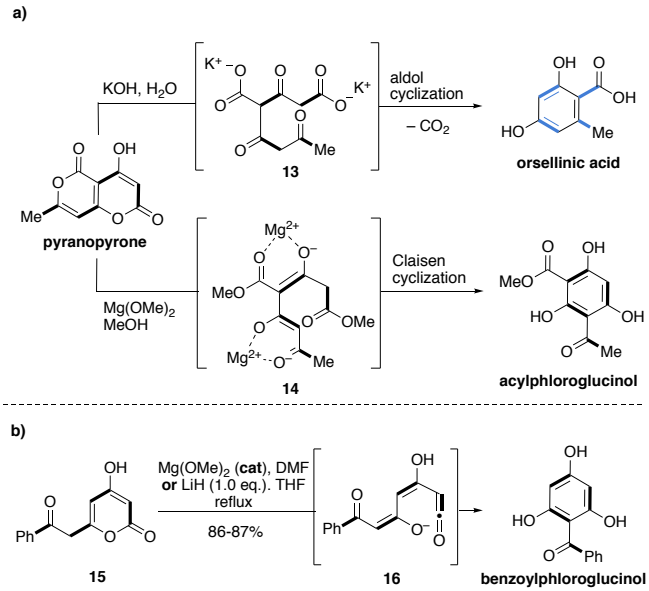


Scheme 5: Collie's biomimetic synthesis of orcinol from dimethylpyrone.

A. J. Birch, a former co-worker of Sir. R. Robinson, underpinned this biosynthetic hypothesis by feeding fungi with ^{14}C labelled acetate, which resulted in the isolation of aromatic natural products with the polyketide-specific labelling pattern.[22] In 1963, Birch and co-workers reported an elegant first synthetic preparation of linear penta-β-carbonyl chains and emphasized the potential of these biomimetic substrates for the preparation of various aromatic products by aldol cyclizations.[23]

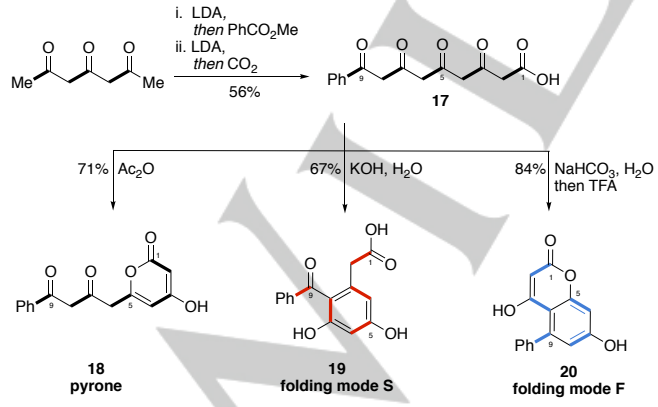
To enable the preparation of the highly reactive intermediates to investigate polyketide cyclizations, Money and Scott studied the in situ synthesis from stable pyrone precursors (Scheme 6a).[24] With the pyranopyrone as a mimic of a tetraketide, stoichiometric amounts of aqueous potassium hydroxide resulted in an aldol cyclization to the fungi-derived natural product orsellinic acid. In contrast, magnesium methoxide in methanol triggered a Claisen cyclization to form acylphloroglucinol. Similar results were obtained by Crombie and James, who proposed that the methyl ester functionality and the chelation of Mg^{2+} leads to an ideal substrate preorganization (**14**) to favor a Claisen condensation.[25] Furthermore, Harris and co-workers proposed a possible

involvement of ketene intermediates (**16**) formed from pyrone substrates (**15**) to explain the high selectivity observed in Claisen cyclizations of a phenyl substituted pyrone-masked tetraketide substrate (Scheme 6b).[26]



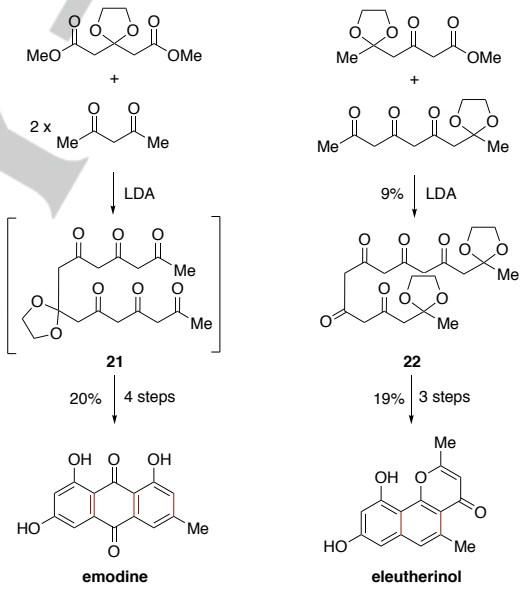
Scheme 6: a) Initial investigations of polyketide cyclizations of tetraketide substrates generated from a pyrone precursor. b) Selective conversion of the pyron protected phenyl tetraketide substrate.

In contrast to the pyrone-masked biomimetic polyketide precursors, Harris and co-workers prepared stabilized poly-β-carbonyl substrates such as the phenyl substituted pentaketide substrate **17** by utilizing Claisen condensations with polyanion species (Scheme 7).[26b,c] Beside the selective formation of the pyrone **18** by activation of the carboxylic acid with acetic anhydride, the divergent preparation of either the folding mode F (**19**) or S (**20**) product was accomplished with stoichiometric amounts of reagents under neutral or basic conditions. The selectivity obtained for the two polyketide cyclizations is proposed to be the result of pH-dependent enol-tautomers.



Scheme 7: Pioneering studies by Harris and co-workers for the regioselective cyclization of the phenyl pent-β-carbonyl substrate to a pyrone and either the folding mode F or S product.

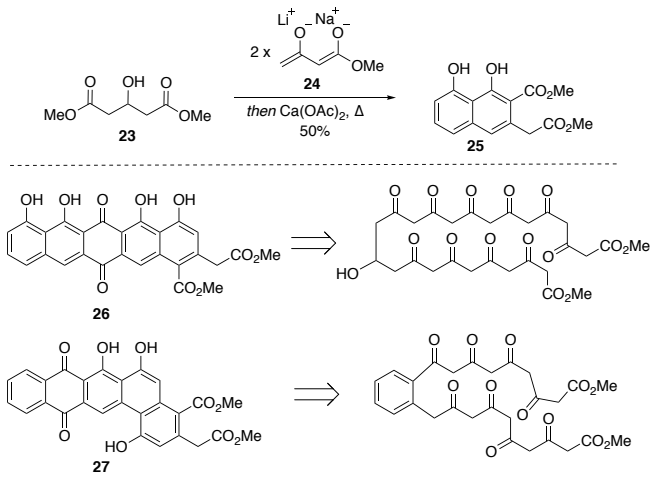
An increased scope for polyaromatic products upon controlling multiple polyketide cyclizations requires poly-β-carbonyl substrates with more than five carbonyl functionalities. Reducing the complexity of cyclizations while increasing the stability of the substrates was accomplished with symmetric substrates that contain protecting groups. Harris and co-workers thus developed polyanion Claisen condensations sequences to access a broad range of natural products derived from protected and reduced hepta-β-carbonyl substrates (Scheme 8).[27] Manipulation of the central carbonyl group by an acetal protecting group resulted in the formation of the anthraquinones emodine by a sequential process over four steps. The protected hepta-β-carbonyl substrate was prepared by a Weiler-type process,[27c] but could not be isolated as it readily converts by a two-fold aldol cyclization. In both cases, a highly regioselective third aldol cyclization was subsequently obtained and by the installation of two terminal acetal protecting groups, the desired substrate for the preparation of the natural product eleutherinol was isolated, although in moderate yield. These results demonstrate the level of control for the folding of poly-β-carbonyl substrates feasible by the introduction of suitable protecting groups and the use of stoichiometric amounts of reagents.



Scheme 8: Protecting group strategies for the selective preparation of the natural products emodine and eleutherinol.

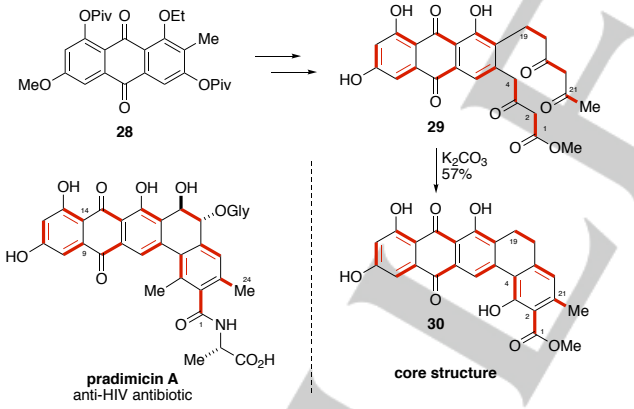
An elegant iterative methodology for the biomimetic preparation of polycyclic polyoxygenated aromatic compounds was implemented by Yamaguchi and co-workers (Scheme 9).[28] The dual Claisen condensation of various diesters (**23**) with acetoacetate dianion (**24**) results in polyketide intermediates, which proceed by a twofold aldol cyclization to form two new aromatic rings mediated by calcium acetate at high temperatures. In a stepwise process, up to pentacyclic aromatic core structures (**25**–**27**) were accessible and the regioselectivity of the aldol cyclizations were found to be substrate-controlled. This methodology was subsequently utilized for the aromatic core structure synthesis of several polyketide natural products, such as urdamicynone B, nanaomycin A or aklavinone and linearly and angularly fused pentacyclic core structures. Moreover, elegant studies by Barrett and co-workers demonstrated that the

polyketide cyclizations can be combined with a cationic polyene cyclization to generate the meroterpenoid natural products (+)-hongoquercin A and B.[29]



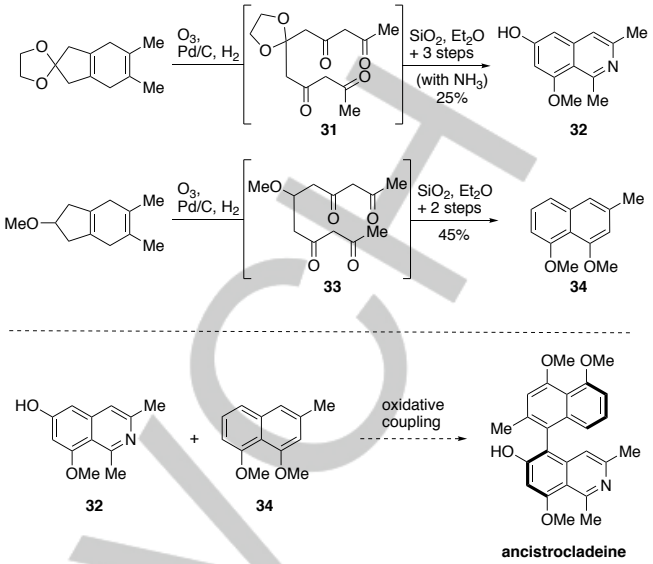
Scheme 9: Preparation of naphthalenoid derivatives following a twofold aldol cyclization process of a reduced hepta-β-carbonyl substrate.

To prepare particularly complex aromatic polyketides, Krohn and co-workers started from an anthrone precursor **28** to synthetically elaborate the installation of two polycarbonyl appendages that induce the folding mode F (Scheme 10, **29**).[30] With the removal of the C19 carbonyl, the twofold aldol condensation selectively proceeds to the angular aromatic dodecaketide core structure **30**, which is represented in pradimicin A.



Scheme 10: Biomimetic approach towards the preparation of pradimicin A.

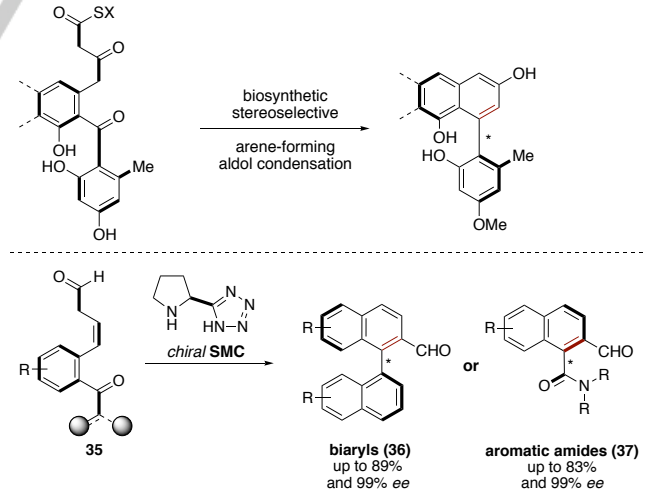
A milder synthesis of poly-β-carbonyl substrates by the Birch strategy[23,30] was utilized by Bringmann and co-workers for the preparation of partially reduced and protected penta-β-carbonyl substrates (**31**, **33**, Scheme 11).[31] Notably, the in situ generated substrates **31** and **33** were converted into two putative precursors (**32**, **34**) involved in the biosynthesis of the atropisomeric ancistrocladeine. The initial polyketide cyclization was triggered by SiO_2, inducing a cascade process to provide the corresponding isoquinoline **32** and naphthalene core structure **34**. Interestingly, a stereo- and regioselective oxidative phenol coupling of these intermediates would provide a unique class of atropisomeric alkaloids.



Scheme 11: Polyketide cyclizations to isoquinoline and the corresponding napthalene intermediate towards the total synthesis of ancistrocladeine.

4. Atroposelective Polyketide Cyclizations

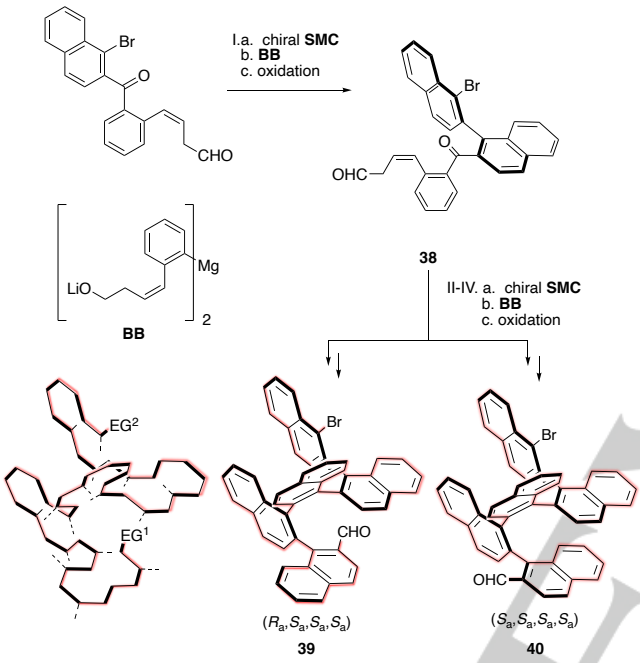
To emulate a stereoselective arene-forming aldol condensation observed in the biosynthesis several rotationally restricted natural products, our group developed a polyketide cyclization catalyzed by small molecule catalysts for the construction of various atropisomeric scaffolds (Scheme 12 cf. Scheme 4).[32] With substrates poised for a polyketide cyclization (**35**) and an activation with suitable catalysts, such as the tetrazole derivative of L-proline, an efficient stereoselective formation of configurationally stable tri-*ortho*-substituted biaryls (**36**, **37**) and atropisomeric aromatic amides was observed.



Scheme 12: The enantioselective arene-forming aldol condensation for the preparation of the tri-*ortho* substituted biaryls (**36**) and atropisomeric aromatic amides (**37**). SMC: small molecule catalyst.

Captivatingly, the transfer of this synthetic strategy from polyketide biosynthesis to small-molecule catalysis provided a means for the preparation of otherwise unrelated topologically

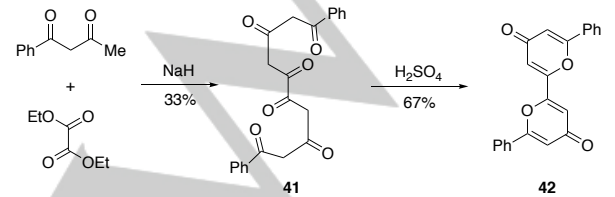
interesting molecular architectures (Scheme 13).[33] The catalyst-controlled aldol condensation followed by the addition of a building block (BB) and in situ oxidation allowed the iterative assembly of configurationally stable, atropisomeric multi-axis systems that formally represent polyketide folds (shown in red). Each stereogenic axis of the oligo-1,2-naphthylene (**38**–**40**) is thereby individually controlled by the small-molecule catalysts, offering an entry into structurally distinct and well-defined molecular scaffolds. Recognizing the prospects of polyketide cyclizations for other fields of application therefore appears as valuable consideration for the retrosynthetic analysis of polyaromatics.



Scheme 13: Stereodivergent synthesis of atropisomeric multiaxis systems by iterative arene-forming aldol condensations controlled by small-molecule catalysts (SMC). BB: building block.

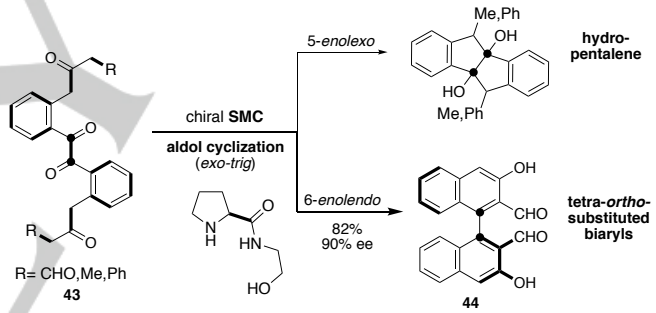
5. Noncanonical Polyketide Cyclization

An oxygenation pattern different from prototypical polyketide natural products (≠β) was recently observed in noncanonical furan derivatives biosynthesized by cryptic polyketide pathways.[34] While this class of polyketides is highly unusual, early investigations by Eiden established a synthesis of 1,2-diketo fused substrate from oxalic acid diester (**41**) and their transformation into noncanonical 2,2'-pyrone derivatives (Scheme 14, **42**).[35]



Scheme 14: Synthesis of 2,2'-bipyrones (**42**) from noncanonical hexa-β-carbonyl substrate.

Notably, the use of small-molecule catalysts in place of polyketide synthases also allows to study catalyst-controlled polyketide cyclizations of noncanonical substrates. For instance, a 1,2-dicarbonyl motif incorporated in a suitable polyketide chain allows to access aromatic polyketide biaryls that are different from oxidative dimerization products. Our studies were therefore focused on hexa-carbonyl substrates with two possible folding modes, leading to 5-*enolexo* or 6-*enolendo* *exo-trig* aldolizations.[36] Captivatingly, a twofold arene-forming aldol condensation thereby gives access to particularly challenging tetra-*ortho*-substituted binaphthalenes with the 3,3'-oxygenation pattern, which is exceptionally valuable to shield reactive centers within a topologically well-defined scaffold. In accord to the pioneering strategies by Birch[23] and Bringmann[31], a mild substrate preparation by a fourfold ozonolysis of readily available biindene precursors allowed the installation of up to six carbonyl functionalities in a single step. The resulting dialdehyde substrates (**43,** R=CHO) were subsequently activated by a catalyst that allows for an extended hydrogen bond network, thus controlling the aldolization mode and the stereoselectivity of the process for biaryls **44**. The utility of the products was recognized by the stereoselective preparation of catalysts, ligands and enantioenriched helicenes, which further underscore the assets of polyketide cyclizations for the assembly polyaromatics, also beyond natural products.



Scheme 15: Noncanonical polyketide cyclization for the atroposelective preparation of tetra-*ortho*-substituted biaryls (**44**) by a twofold aldol cyclization controlled by a chiral small-molecule catalyst (SMC).

6. Conclusion

By following the biosynthetic principles of polyketide assembly, various polycyclic aromatic compounds are accessible by captivating and efficient synthetic strategies. The retrosynthetic identification of the polyketide pattern thus permits to design synthetic methods not only for the total syntheses of natural products, but also for topologically unique molecular architectures valuable for otherwise unrelated applications. Next to polyketide cyclizations to construct the polyaromatic core structures of pharmacologically valuable natural products and derivatives, catalyst scaffolds and helical polyaromatics are readily accessible from poly-β-carbonyl precursors. The strategic and mild preparation of those highly reactive substrates thus represents an essential prerequisite to transfer polyketide reactivity principles to develop biomimetic synthetic methods. The high reactivities of more complex polyketone precursors and the multitude of cyclization pathways likely requires stabilizing templates that

prefold the polyketide chains. Similar to polycyclization strategies for other natural product families such as the terpene cyclase mimics,[37] selective catalytic activation modes that control the folding of increasingly complex substrate chains can be anticipated for the divergent construction of natural und new-to-nature carbon frameworks by the cyclization of common polyketide intermediates.

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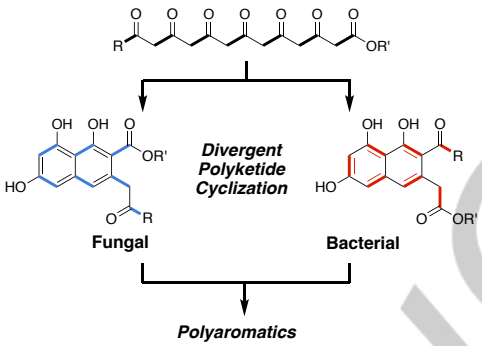
REVIEW

The folding and cyclization of polyketide chains precisely controls the divergent biosynthesis of structurally distinct aromatic natural products. In this minireview, we highlight the virtues of transferring this biosynthetic concept into the assembly of polyaromatics and underline the prospects of emerging divergent cyclizations controlled by small molecules catalysts.



*Vincent C. Fäseke, Felix C. Raps, Christof Sparr**

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